

Direct Cleavage of Internal Epoxides with Periodic Acid¹

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Abstract

Reaction of methyl esters of epoxidized fatty acids with paraperiodic acid led to direct cleavage of epoxide functions and the production of aldehydes and methyl azelaaldehyde. The reaction was carried out in aqueous dioxane. The use of other solvents and the influence of reaction variables was examined. The reaction is essentially quantitative for methyl 9,10-epoxystearate.

Introduction

THE USE OF PERIODIC ACID as an oxidant for 1,2-glycols was introduced by Malaprade (1,2) in 1928. Since that time the acid has been used extensively as an analytical reagent to test qualitatively for the presence of, or to measure quantitatively the amount of, 1,2-glycols, 1,2-amino-alcohols, 1,2-diketones, α -keto aldehydes or α -hydroxy ketones (3). Probably the best-known example of this analytical application is the use of periodic acid in the determination of monoglycerides (4). Moreover, periodic acid has been used to generate the aldehydes which are directly derivable from the above oxygenated compounds by carbon-carbon bond cleavage. For instance, King (5) has subjected 9,10-dihydroxystearic acids to periodic acid cleavage to prepare pelargonic aldehyde and azelaaldehydic acid. The reaction of Malaprade has found another application in the field of structure proof, particularly of natural products. Gunstone (6) used periodic acid in proving the structure of an oxygenated acid found in *Camelina sativa* seed oil, and Gunstone and others applied similar procedures to determine the structures of other vicinal glycols.

In spite of the rather voluminous literature regarding the use of periodic acid in the cleavage of 1,2-glycols and related compounds, the application of this reagent to the cleavage of 1,2-epoxides has been ignored almost entirely. The analysis of ethylene oxide with dilute periodic acid was reported in 1950 (7) but was not extended to other epoxides. Two years later a general qualitative test for epoxides was proposed (8) using periodic acid acidified with nitric acid, but again further amplifications are lacking. Thus in the absence of a suitable direct cleavage method for epoxy groups, their locations on hydrocarbon chains of such naturally occurring acids as vernolic acid (8) and coronaric acid (9) were determined by first converting the oxirane groups to 1,2-diols, then treating the latter with periodic acid.

During the course of some epoxidation studies in progress in our laboratory the need developed for a direct cleavage method to demonstrate the location of oxirane groups. The present work describes a study of the reaction of some oxirane compounds with periodic acid to produce aldehydes. The method of choice involves treatment of a dioxane solution of the epoxide with aqueous periodic acid at room temperature and extraction of the reaction products from an aqueous suspension with petroleum ether. After removal of the solvent the reaction products are analyzed by GLC and IR spectroscopy.

Experimental Procedures and Data

Materials Used

Methyl 9,10-epoxystearate. Prepared by epoxidation of methyl oleate as reported previously (10).

Methyl 9,10:12,13-diepoxysearate. To 70.0 g (0.238 moles) of methyl linoleate (I.V. 172.4) in 500 ml chloroform was added 112.0 g of 35.4% per-acetic acid in acetic acid (0.521 moles peracetic acid) in which 5.6 g sodium acetate trihydrate had been dissolved. The addition was carried out over a period of 20 min with agitation while the reaction temperature was controlled at 27–29°C by means of a cooling bath. After addition was complete the reaction mixture was stirred for 3½ hr at room temperature and was then washed successively with 2 × 300 ml water, 300 ml sodium bicarbonate solution (2%), and again 2 × 300 ml water. The chloroform solution was then dried over CaSO₄ and evaporated to obtain 72.3 g crude oil, oxirane oxygen 9.06% (Theory 9.80%), I.V. 2.23. Crystallization of the crude material (70.0 g) from 350 ml Skellysolve B at –30°C and collection of the crystals gave 39.6 g of solid diepoxide, oxirane oxygen 9.49% (Theory 9.80%). Recrystallization of the solid from either Skellysolve B or acetone did not improve its oxirane content.

Methyl 12-Hydroxy-9,10-Epoxysearate. To a solution of 15 g (0.048 mole) of methyl ricinoleate (98+ % pure by GLC) in 120 ml chloroform was added, with stirring, 12 g of a 40% solution of peracetic acid in acetic acid (0.063 moles peracetic acid) containing 0.6 g sodium acetate trihydrate. Dropwise addition was carried out over a period of 1 hr at 24–26°C. The mixture was stirred at room temperature for 3 hr and was then washed successively with 60 ml water, 3 × 30 ml aqueous sodium sulfite solution (2%), and 3 × 30 ml water. The chloroform solution was dried over CaSO₄ and evaporated to an oily residue (15.0 g). Oxirane oxygen, 4.84% (Theory 4.87%).

Methyl Vernolate. In general the preparative method of Luddy and Barford (11, 12) was followed in converting trivernolin to methyl vernolate. A solution of sodium methoxide in methanol was prepared by adding 1.2 g sodium metal to 2060 ml of dry, redistilled methanol. To this solution was added 201 g trivernolin supplied kindly by C. F. Krewson. The reaction mixture was refluxed for 15 min, cooled to room temperature, brought to pH 3.5 with cold dilute sulfuric acid and diluted with 100 ml water. The mixture was extracted repeatedly with petroleum ether (bp 40–60°C) and the combined extracts were washed with water, dried over Drierite, filtered, and evaporated on a rotating evaporator to obtain 188 g crude methyl vernolate. Oxirane oxygen; 4.64% (Theory 5.15%). GLC analysis indicated several impurities including some methyl ketostearate and/or methyl hydroxystearate. The crude material was further purified by column chromatography on silica gel to give methyl 12,13-epoxy-9-octadecenoate; oxirane oxygen, 4.97% (purity by oxirane; 96.5%). GLC indicated that a small amount of residual solvent was the principal impurity.

Dimethyl Sebacate. This material was required as internal standard for GLC. Sebacic acid was esterified according to the method of Lough (13).

¹ Presented at the AOCS Meeting in Cincinnati, October 1965.

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is actually a hydration reaction, i.e., the conversion of the oxirane group to a glycol group catalyzed by periodic acid and requiring water as a reagent. Such a hydration would be quite reasonable in the light of our earlier work (10, 16) concerned with hydrations. However, additional information now accumulating in our laboratory seems to indicate that the glycol is not likely to be an intermediate, at least in the cleavage of methyl 9,10:12,13-diepoxysearate.

If too much water is present in the mixture, the reaction again goes incompletely. When five times the usual amount of water was added, i.e., 1.25 g H_2IO_6 in 10 ml water instead of the usual 2 ml, only about 4% of the methyl 9,10-epoxysearate was cleaved during the usual 15-min period while the balance was recovered intact. Again, a reasonable explanation for this behavior seems to be lack of suitable contact between reagents. The acid is dissolved in a large aqueous dioxane phase while the epoxyester, dissolved in some dioxane, floats on top as a separate layer. The two phases are quite immiscible when the water content of the lower layer is high.

Only a brief period of time is required for the cleavage reaction to go to completion at room temperature. The 15-min period which is usually allowed is more than sufficient, and the amount of unreacted methyl 9,10-epoxysearate remaining after that period is usually less than 1%. On the other hand it was demonstrated experimentally that the aldehyde products are stable under the reaction conditions used, so that a longer reaction period is not harmful. Little is known about the minimum time requirement of the periodic acid cleavage of epoxides, but qualitatively the reaction seems to be slower than the cleavage of the corresponding vicinal glycol. When methyl 9,10-epoxysearate dissolved in dioxane is mixed with an aqueous solution of paraperiodic acid under the conditions described in the experimental section, a two-phase system forms. The lower and much larger layer contains water, dioxane and periodic acid while the smaller upper layer contains the epoxy ester and some dioxane. During the first minute or two of agitation the reaction mixture becomes clear and homogeneous. After another brief period of stirring, the mixture again becomes cloudy and finally crystals, presumably iodic acid, separate. When methyl 9,10-dihydroxysearate is treated under identical conditions a homogeneous mixture forms instantaneously, but this mixture clouds up at once with the separation of iodic acid.

In the absence of the experimental confirmation, one can only speculate regarding the mechanism of the cleavage reaction of epoxides. It seems reasonable, however, that the epoxide and the glycol form identical cyclic intermediates (17), but that the epoxide forms this intermediate more slowly than the glycol. It is probably the formation of the cyclic intermediate which is observed when the initial 2-phase system becomes a homogeneous solution.

The effect of reaction temperature upon yields was tested at room temperature, 50C and 85C. Results which are summarized in Table II, indicate that at elevated temperature the yields are lower and erratic because of further reaction and polymerization of the aldehyde products.

The choice of drying agent affected the yield of cleavage products materially. When equal portions of reaction products were dried over Na_2SO_4 , $CaCl_2$ and $CaSO_4$, the first two drying agents were found to give equal yields while $CaSO_4$ gave 20% lower yields.

TABLE II
Periodic Acid Cleavage of Methyl 9,10-Epoxysearate:
Effect of Reaction Temperature

Temp, C	Methyl azelaaldehyde yield, %
25	89.1
50	37.8
50	42.4
85	59.3
85	67.5

Periodate salts, e.g., potassium periodate, are not effective replacements for periodic acid in the cleavage epoxides although vicinal glycols are readily cleaved by such salts. Thus methyl 9,10-epoxysearate dissolved in dioxane or acetone was not affected by potassium periodate. This is as expected if the first step of the cleavage reaction is an acid catalyzed ring opening, followed or perhaps accompanied by nucleophilic attack of periodate anion on an oxirane carbon atom.

The reaction conditions described in this paper are particularly suitable for the periodic acid oxidation of internal epoxides. Some other types of oxirane compounds resist cleavage under these conditions or isomerize to carbonyl compounds. For example, phenyl glycidyl ether, when subjected to periodic acid treatment, isomerized presumably to phenyl acetone, and only traces of aldehydic materials could be found among the products. Glycidyl searate, on the other hand, did not react with periodic acid in dioxane, and more than 80% of the starting material was recovered. This compound, however, was oxidized almost quantitatively to formaldehyde and formyl-methyl searate when treated with a large excess of periodic acid dissolved in a mixture of acetic acid and chloroform (18). Tertiary epoxides were not cleaved by periodic acid but isomerized instead. Vinyl cyclohexene dioxide reacted vigorously to yield a product which appeared to result from the interaction of the two oxirane groups.

Yields of cleavage products were estimated with fair accuracy by GLC using dimethyl sebacate as internal standard. An alternate and less accurate method of calculating cleavage yields consisted of evaporating the product mixture to a low pelargonic aldehyde content and estimating the methyl azelaaldehyde content of the sample by direct GLC analysis. The latter method was sufficiently accurate when relative yields were of interest, i.e., when the effect of the reaction variables was evaluated.

ACKNOWLEDGMENTS

S. F. Herb and P. Magidman provided helpful discussions of GLC techniques. E. J. Saggese carried out the cleavage of glycidyl searate.

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[Received September 7, 1965]

TABLE I
Periodic Acid Cleavage of Methyl
9,10-Epoxystearate in Various Solvents

Solvent	Methyl azelaaldehyde Yield, % ^a
1,4-Dioxane	89.1
Nitromethane	89.9
Methyl Acetate	77.6
Acetic Acid	47.7

^a Yields calculated by the less accurate evaporation method entailing loss of cleavage product (see discussion).

1,4-Dioxane. 1,4-Dioxane (Eastman-practical) was purified according to the method of Hess and Frahm (14).

All other solvents and chemicals were used as purchased.

Procedures

Periodic Acid Cleavage of Methyl 9,10-Epoxy-stearate. To a solution of 1.25 g (0.0548 mole) paraperiodic acid (H_5IO_6) dissolved in 2 ml water was added a solution of 1.00 g (0.00317 mole) methyl 9,10-epoxystearate (99% pure) in 10 ml purified 1,4-dioxane. The mixture was stirred at room temperature for 15 min and was then poured into 100 ml water. The aqueous mixture was extracted with two 25 ml portions of petroleum ether (bp 35–60°C), and the combined extracts were washed with 10 ml water, dried over anhydrous sodium sulfate and evaporated under nitrogen to obtain an oily residue (1.32 g). To this residue was added 0.243 g dimethyl sebacate as internal standard, and the mixture was analyzed by GLC. Results of the GLC analysis indicated that the cleavage product contained 0.00319 mole methyl azelaaldehyde in addition to considerable amounts of pelargonic aldehyde and solvent. It was therefore concluded that the reaction had proceeded quantitatively.

Repetition of the cleavage reaction on a fivefold scale followed by isolation of the cleavage products and chromatography of the latter on silica gel (Davison No. 923) led to isolation of methyl 8-formyl-octanoate (methyl azelaaldehyde), purity > 99% by GLC and TLC, $n_D^{20} = 1.4360$ [lit (15): $n_D^{20} = 1.4344$].

Periodic Acid Cleavage of Methyl 12-Hydroxy-9,10-Epoxystearate. To 1.25 g (0.00548 g) paraperiodic acid in 2 ml water was added 1.00 g (0.00303 mole) methyl 12-hydroxy-9,10-epoxystearate dissolved in 10 ml purified 1,4-dioxane. The mixture was stirred for 15 min at room temperature and was then poured in 100 ml water. The aqueous mixture was extracted with three 25 ml portions petroleum ether, and the combined extracts were washed with 10 ml water and dried over sodium sulfate. To the dried solution was added 0.227 g dimethyl sebacate as internal standard and the solution was then evaporated under nitrogen. The evaporation residue (1.47 g) was analyzed by GLC and was found to contain 0.00251 mole methyl azelaaldehyde. Yield: 82.8%.

Periodic Acid Cleavage of Methyl 9,10:12,13-diepoxystearate. To 1.25 g (0.00548 mole) paraperiodic acid in 2 ml water was added 0.50 g (0.00150 mole) methyl 9,10:12,13-diepoxystearate dissolved in 10 ml purified 1,4-dioxane. The mixture was stirred for 15 min at room temperature and was then poured into 100 ml water. The aqueous mixture was extracted with three 25 ml portions petroleum ether, and the combined extracts were washed with 10 ml water and dried over sodium sulfate. The dried solution was evaporated to an oily residue (0.33 g) which was found (by GLC) to contain 0.21 g methyl azelaaldehyde. Yield: 75%. Other samples which had been evaporated less completely also contained signi-

ficant amount of hexanal, identified by GLC. The principal byproduct appeared to be a single compound having a longer GLC retention time than the diepoxide starting material.

Periodic Acid Cleavage of Methyl Vernolate (Methyl 12,13-Epoxy-9-Octadecenoate). To a solution of 1.25 g (0.00548 mole) paraperiodic acid in 2 ml water was added 1.00 g (0.00322 mole) methyl vernolate dissolved in 10 ml purified 1,4-dioxane. The reaction was carried out and the products were isolated in the manner described for methyl 9,10:12,13-diepoxystearate to obtain an oil (0.79 g) containing three closely related products (0.44 g) assumed to be isomers of methyl 11-formylundecenoate. Yield: 60%. Increase of reaction time to 1 hr decreased the yield to 46.8%.

GLC Analyses. All GLC analyses were carried out on an F & M No. 720 dual column gas chromatograph equipped for temperature programming and provided with an automatic attenuator-integrator. Separations were carried out on 2 ft $\frac{1}{4}$ in. O.D. columns packed with 10% XE-60 on Diatoport or with 15% SE-30 on Diatoport. The helium flow was 50 ml/min. Analyses were either carried out isothermally at 200°C, or the temperature was programmed from 80°C to 270°C at 5°C/min. Quantitation of results was obtained by the use of dimethyl sebacate as internal standard. Correction factors were calculated from gas chromatograms of mixtures of internal standard and known pure reference compounds, determinations being carried out in triplicate. Correction factors had to be determined daily as reported by others (15).

Discussion

For the direct cleavage of methyl 9,10-epoxystearate with periodic acid a reaction medium is preferred which dissolves both the polar periodic acid and the rather nonpolar ester. Ease of isolation and analysis of the cleavage products makes it desirable that the solvent used for this reaction is relatively volatile and inert under the reaction conditions.

The cleavage may be carried out in any of several solvents, as summarized in Table I, but yields vary somewhat. Acetic acid is the least suitable of the four solvents listed, because of its tendency to add to oxirane compounds to form acetoxy hydroxy derivatives. This side reaction was observed whenever acetic acid was the solvent, even when the reaction was carried out at low temperature. Cleavage also occurred in high yield when the reaction was carried out in methanol or ethanol, but the principal products were acetals and hemiacetals rather than aldehydes. Less polar solvents such as toluene, petroleum ether and ethyl ether were unsuitable as reaction media and little or no aldehyde was obtained. Use of acetone resulted in epoxide cleavage but was considered objectionable since lachrymatory byproducts were formed, apparently by interaction of periodic acid with the solvent. The work reported here is based almost exclusively on a dioxane solvent system.

The amount of water present is an important variable when methyl 9,10-epoxystearate dissolved in 1,4-dioxane is treated with periodic acid. In the absence of added water the reaction proceeded very slowly, and after the usual 15-min reaction period 88% of unreacted starting material was recovered. One possible explanation for this lack of activity in the absence of added water may be found in the poor solubility of periodic acid in dioxane which resulted in poor contact between reagents. Another explanation may be that the first step in the cleavage reaction